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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,386	11/17/2005	Heike Gielen-Haertwig	Le A 36 266	2246

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EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	**PAPER NUMBER**
1624	

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03/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,386	GIELEN-HAERTWIG ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16,17,19,21-25,27 and 28* is/are pending in the application.

4a) Of the above claim(s) *13,15,16,19,21-25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/10/2005 & 1/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to a restriction election filed on January 2, 2008. There are twenty-five claims pending and fourteen claims under consideration. Claims 18, 20, 26 and 29 were cancelled. Claims 13, 15, 16, 19, 21-25, 27 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The applicants have elected Group I **without** traverse. This is the first action on the merits. The present invention relates to novel heterocyclic derivatives, processes for their preparation, and their use in medicaments, especially for the treatment of chronic obstructive pulmonary diseases, acute coronary syndrome, acute myocardial infarction and heart failure development.

2. Certain claims in the previous restriction requirement were assigned to both Groups I and II when they should have been assigned to *either* Group I or Group II. Claims 12, 14, 16 and 17 cover compounds or compositions of general formula (I-A) only, while claims 13, 15, and 23 cover compounds or compositions of general formula (I-B) only. The following is a reorganized list of the Groups from the restriction requirement with the proper claims located in the proper Restriction Groups:

I. The compound or composition of general Formula (I-A), wherein A is a phenyl ring, R^2 is a cyano group, Y^1, Y^2, Y^3, and Y^4 are -CH-, and either R^3 or R^7 is H, according to Claims 1-12, 14, 16, 17 and 21.

II. The compound or composition of general Formula (I-B), wherein A is a phenyl ring, R^2 is a cyano group, Y^1, Y^2, Y^3, and Y^4 are -CH-, and either R^3 or R^7 is H, according to Claims 1-11, 13, 15, and 23.

III. The compound or composition of general Formula (I-A) or (I-B), which was not described in Groups I or II, according to Claims 1-15, 17 and 23.

IV-VI. The process for synthesizing a compound or composition of general Formula (I-A) or (I-B) according to Groups I-III, wherein A is a phenyl ring, R^2 is a cyano group, Y^1, Y^2, Y^3, and Y^4 are -CH-, and either R^3 or R^7 is H, according to Claim 16, 19 and 25.

VII-IX. The method of treatment with a compound or composition of general Formula (I-A) or (I-B) according to Groups I-III, wherein A is a phenyl ring, R^2 is a cyano group, Y^1, Y^2, Y^3, and Y^4 are -CH-, and either R^3 or R^7 is H according to Claims 21, 22, 24, 27, and 28.

Priority

3. Acknowledgment is made of Applicant's claim for foreign priority. This application, U.S. Application No. 10/527,386, filed on March 10, 2005, claims foreign priority to British Application No. 0311957.3, filed on May 23, 2003 and British Application No. 0220961.7, filed on September 10, 2002.

Specification

4. Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

6. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

7. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

8. Claims 1-12, 14 and 17 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Due to the restriction election made by applicants, Claims 1-12, 14 and 17 contain non-elected subject matter. Appropriate corrections are necessary.

Claim Rejections - 35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-12, 14 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of Formula (I-A) where

R^1 is a hydrogen or an alkyl group; R^2 is a cyano group; R^4 is a C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, or a mono- or di-C_1-C_4-alkylaminocarbonyl group, R^5 is a methyl group; R^{6A} is a hydrogen, C_1-C_6-alkylcarbonyl, C_3-C_8-cycloalkylcarbonyl group; and R^7 is a trifluoromethyl or halogen group, does not reasonably provide enablement for any other compounds or compositions not previously defined by the R variables. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the compounds and compositions of the invention commensurate in scope with these claims.

11. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds of Formula (IA) where the R variables are other than those previously mentioned. Applicant has only shown a select number of compounds or compositions within the specification and of these, none of them fall outside of the

scope of enablement mentioned here.

2) Unpredictability in the art. Chemistry is unpredictable. See *In Re Marzocchi and Horton* 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)..." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

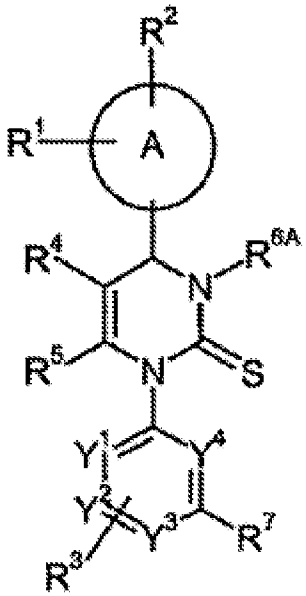
The scope of any compounds where the R variables are not those previously described above is not adequately enabled or defined. Applicants have provided no guidance as how the compounds are made more active *in vivo*.

3) *Number of working examples*. Applicant has provided no working examples of any compounds or compositions where the R variables are other than those described above. "Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each

member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p). There is no guidance or direction to consider disclosures in the art to prepare the diverse compounds and compositions instantly claimed. Applicants bear the responsibility to teach how to make the compounds set forth in their claims.

4) *Nature of the invention*. The nature of this invention relates to novel heterocyclic derivatives, processes for their preparation, and their use in medicaments, especially for the treatment of chronic obstructive pulmonary diseases, acute coronary syndrome, acute myocardial infarction and heart failure development.

5) Scope of the Claims. The scope of the claims is all of the tens of thousands of compounds represented by general formula (I-A):



thus the scope of the claims is very broad.

6) *Level of skill in the art*. The artisan using Applicants invention would be a chemist with a M.S. or Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

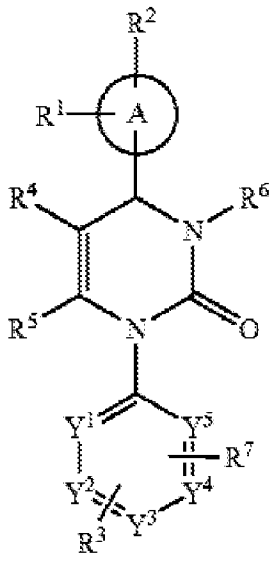
F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

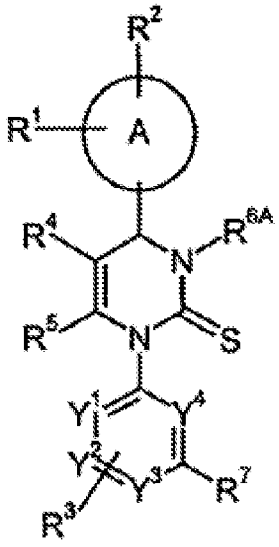
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-12, 14, and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 and 14 of U.S. Patent Publication Application No. 2008/0021053 in view of *Graver Tank & Mfg. Co. v. The Linde Air Products Co*, (USSC 1950) 339 US 695, 85 USPQ 328.

The published reference, 2008/0021053, a U.S. Patent application that teaches compounds of the general formula (I):



Whereby ring A can be a phenyl ring and Y^1-Y^5 can be CH groups, forming a second phenyl ring. The U.S. Patent Publication Application No. 2008/0021053 reference teaches the same compounds as the current application except for one main difference. The current application teaches compounds of formula (I-A):



The difference is in the 2 position of the pyrimidine, where the published reference teaches a 2-one derivative, while the current application teaches a 2-thione derivative. Both applications state the compounds or compositions can be used in medicaments, especially for the treatment of chronic obstructive pulmonary diseases, acute coronary syndrome, acute myocardial infarction and heart failure development.

The court decision of Graver Tank teaches that *the important factor in determining a test for equivalency in a prior art document is whether a person who is reasonably skilled in the art would recognize the equivalency in the compound or composition*. In *Ex parte Wiseman* (POBA 1953) 98 USPQ 277, a difluorinated compound was held unpatentable over the prior art dichloro compound on the basis of analogical reasoning. A compound need not be an adjacent homolog or position isomer of a prior art compound in order to be susceptible to a rejection based on structural obviousness; the name used to designate the structural relationship between compounds is not controlling, it is the closeness of that relationship. In *re Payne et al.* (CCPA 1979) 606 F2d 303, 203 USPQ 245. When chemical compounds have "very close" structural similarities and similar utilities, without more, a *prima fade* case of obviousness may be made. *In re Grabiak* (CAFC 1985) 769 F2d 729, 226 USPQ 870.

Relating the information from Graver Tank to the current 2008/0021503 publication, it would have been obvious for a person of ordinary skill in the art to attempt the same process and replace the carbonyl group of the 2-position in the pyrimidine with a thione derivative to synthesize a pyrimidin-2-thione in the same position. The use for these compounds and compositions as medicaments is identical, and the residue

groups of the prior art and the application are so similar that one skilled in the art would expect that any differences would be inconsequential in the final product. The difference between sulfur and oxygen are well known in the chemical arts to have similar properties. For example, both elements fall within the same family in the periodic table of the chemical elements. As atoms, both oxygen and sulfur contain the same valence number, similar chemical properties and numerous chemical literature has suggested the attempted use of a thiol over an alcohol or a thiourea in place of a urea and vice versa. Due to the numerous chemical property similarities of oxygen and sulfur, this substitution would be attempted by anyone skilled in the art.

It would have been obvious to one skilled in the arts at the time of the invention to be motivated to synthesize the same compounds or compositions with a pyramid-2-thione instead of a pyrimidin-2-one. The patent publication shows a pyrimidin-2-one and Graver Tank shows that a C(=O) group is equivalent to a C(=S) group and that any of these derivatives would be chemical equivalents, and thus would not alter or affect the claimed compounds in any way. Due to the numerous chemical property similarities of sulfur and oxygen, this substitution would be attempted by anyone skilled in the art who was attempting to make pyrimidin-2-thiones. The claims above are obvious because the substitution of one known element for another (sulfur for oxygen) would have yielded predictable results in the process to one of ordinary skill in the art at the time of the invention.

This is a provisional obviousness-type double patenting rejection.

Conclusion

14. Claims 1-12, 14, and 17 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a US PTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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